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DOCUMENT-IDENTIFIER: US 5759573 A
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TITLE: Cyclodextrin liposomes encapsulating pharmacologic compounds and methods for their use

Abstract Text (1):
Liposomes containing cyclodextrin in the encapsulated aqueous phase are useful for encapsulation of biologically active substances, especially those which are hydrophilic. The encapsulated cyclodextrin facilitates a slow, controlled release of pharmacologic compounds from the liposomes. The novel methods of the present invention allow the treatment of a variety of pathophysiological states by administering the cyclodextrin-containing liposomes encapsulating the pharmacologic compounds. The present invention also provides a novel method of extending the half life of a pharmacologic compound in an animal.

Brief Summary Text (7):
Liposome delivery systems have been proposed for a variety of pharmacologically active compounds including antibiotics, hormones and anti-neoplastic agents (Liposomes, 1983, Marc J. Ostro, Ed., Marcel-Dekker, Inc., New York, 1983). The use of liposomes to encapsulate pharmacologic agents and the efficacy of liposomal delivery systems differs according to the water-and lipid-solubility of the drug. For example, hydrophilic substituted for encapsulation in multivesicular liposomes. In contrast, hydrophobic, water insoluble compounds tend to be incorporated into the lipid bilayer. These compounds, therefore, are not well suited for encapsulation into the aqueous internal chambers of a liposome delivery system. The cyclodextrin class of compounds, especially .beta.-cyclodextrin, has been used successfully to solubilize water-insoluble hydrophobic compounds (Strattan, January 1992, Pharm. Tech. 68-74; Strattan, February 1992, Pharm. Tech. 52-58; Stern, DN&P, 2:410-415, 1989; Pagington, Chem. Brit. 23:455-458, 1987).

Brief Summary Text (12):
In one embodiment of the present invention, there is provided a liposome composition, comprising a water soluble compound encapsulated in said liposome, wherein said liposome composition contains encapsulated cyclodextrin.

Brief Summary Text (13):
In another embodiment of the present invention, there is provided a method of treating a pathophysiological state in an individual comprising administering a liposome composition to the individual, said composition comprising a pharmacologically effective amount of a water soluble compound encapsulated in said liposome, wherein said liposome composition contains encapsulated cyclodextrin.

Brief Summary Text (14):
In yet another embodiment of the present invention, there is provided a method of increasing the half-life of a compound in an animal comprising the step of administering an admixture of liposomes encapsulating the compound, wherein said liposome encapsulates cyclodextrin.

Brief Summary Text (19):
The term "MVL-CD-MTX" means a formulation containing methotrexate encapsulated into

multivesicular liposomes in the presence of cyclodextrin.

Drawing Description Text (3):
FIG. 1 shows the concentrations of methotrexate in cerebrospinal fluid (CSF) after intracisternal injection of 100 .mu.g (0.22 .mu.mol) of multivesicular liposomes encapsulating methotrexate and cyclodextrin (MVL-CD-MTX) (closed circle, free; open square, total) or as unencapsulated methotrexate (closed square). Each data point represents mean and standard deviation from three rats.

Drawing Description Text (10):
FIG. 8 shows the intraperitoneal concentrations of methotrexate after intraperitoneal injection of 10 mg/kg (22 .mu.moles/kg) of methotrexate as unencapsulated methotrexate (open circles), unencapsulated cyclodextrin-methotrexate complex (shaded triangles) or multivesicular liposome encapsulated methotrexate, MVL-CD-MTX (shaded circles, free; open boxes, total). Each point represents the mean and the standard deviation from a group of three mice.

Drawing Description Text (11):
FIG. 9 shows the amounts of methotrexate remaining within the peritoneal cavity after injection of 10 mg/kg (22 .mu.moles/kg) of methotrexate as unencapsulated methotrexate (open circles), unencapsulated cyclodextrin- methotrexate complex (closed triangles) or multivesicular liposome encapsulated methotrexate, MVL-CD-MTX (shaded boxes). Each point represents the mean and the standard deviation from a group of three mice.

Detailed Description Text (2):
The present invention is directed to forming inclusion complexes of water-soluble compounds, such as methotrexate, with cyclodextrins, preferably .beta.-cyclodextrin, and to encapsulating the inclusion complex into liposomes for controlled release. For use in the practice of this invention the cyclodextrin preferably forms an inclusion complex with the water soluble compound wherein the apolar cavity of the cyclodextrin is occupied by or sequesters the compound sufficiently to slow the rate of release from the liposome composition. The rim or the periphery of the inclusion complex is hydrophilic with the result that the inclusion complex forms a solution in aqueous media. The cyclodextrin-complexed water soluble substance can then be encapsulated into liposomes.

Detailed Description Text (3):
In addition to preventing incorporation of water soluble compounds into the lipid layers of the liposomes during their formation, Applicants have discovered that formation of an inclusion complex results in a reduction in the rate of release of the hydrophilic compound from the liposome compared to the rate of release of the same compound encapsulated in the absence of the cyclodextrin.

Detailed Description Text (4):
The present invention provides a liposome composition, comprising a pharmacologically active amount of a biologically active compound encapsulated in said liposome, wherein said liposome composition further contains encapsulated cyclodextrin. Preferably, the biologically active compound is water soluble. In the practice of this invention, the water soluble compound generally has water solubility of greater than about 1 .mu.g/ml, preferably greater than about 100 .mu.g/ml, and most preferably greater than about 1 mg/ml, in the absence of cyclodextrin.

Detailed Description Text (6):
Cyclodextrins are chiral, toroidal-shaped molecules formed by the action of the enzyme cyclodextrin transglycosylase on starch. These cyclic oligomers contain from 6 to 12 glucose units bonded through .alpha.-(1,4)-linkages. The three smallest homologs, .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin are available commercially; larger homologs must be produced and isolated individually.

The secondary 2- and 3-hydroxy groups line the mouth of the cyclodextrin cavity and have a staggered orientation. The primary 6-hydroxyls are at the opposite end of the molecule. The inside of the cyclodextrin cavity is relatively hydrophobic since all hydroxyls are directed toward the outside of the molecule.

Detailed Description Text (7):
It is specifically contemplated that many different types of cyclodextrins would be useful in the compositions and methods of the present invention. For example, the present invention may use natural .alpha.-, .beta.- or .gamma. cyclodextrins. Similarly, the present invention may utilize semisynthetic substituted cyclodextrins such as; methyl cyclodextrins, ethyl cyclodextrins, hydroxyethyl cyclodextrins, hydroxypropyl cyclodextrins, branched cyclodextrins, cyclodextrin polymers or monosuccinyl dimethyl .beta.-cyclodextrin. Most preferred for the compositions and methods of the present invention is 2-hydroxypropyl-.beta.-cyclodextrin.

Detailed Description Text (8):
Generally, the concentration of cyclodextrin used in preparing the liposomes of the present invention is that which slows the release of a pharmacologic compound from the liposome after administration to an animal. Preferably, the cyclodextrin is present in the liposome composition in an amount of from about 10 milligrams per ml to about 400 milligrams per ml. More preferably, the amount of cyclodextrin in the liposome is about 100 mg/ml.

Detailed Description Text (9):
Generally, the liposome of the present invention may be any that when prepared with encapsulated cyclodextrin provides slow, controlled release of pharmacologic compounds. Preferably, the liposome is selected from the group of unilamellar, multilamellar and multivesicular liposomes. Most preferably, the liposome is a multivesicular liposome.

Detailed Description Text (10):
Generally, the biologically active compound encapsulated in the liposome oil the present invention may be any whose release rate from a liposome encapsulating cyclodextrin is slower than that in the absence of the cyclodextrin. Therapeutic biologically active compounds may be selected from the general group consisting of anti-neoplastic agents, anti-infective agents, anti-depressives, antiviral agents, anti-nociceptive agents, anxiolytics and hormones.

Detailed Description Text (17):
Representative examples of anti-nociceptives useful in the compositions and methods of the present invention include hydromorphine, oxycodone, fentanyl, morphine and meperidine.

Detailed Description Text (19):
The present invention also provides a method of increasing the half-life of a pharmacologic compound in an animal comprising the step of administering an admixture of liposomes encapsulating the pharmacologic compound, wherein said liposome further encapsulates cyclodextrin.

Detailed Description Text (20):
The present invention additionally provides a method of treating a pathophysiological state in an individual comprising administering a liposome composition to the individual, said composition comprising a therapeutically effective amount of a compound encapsulated in said liposome, wherein said liposome composition further encapsulates cyclodextrin. The term "therapeutically effective" as it pertains to the compositions of the invention means that biologically active therapeutic agent is present in the aqueous phase within the vesicles at a concentration sufficient to achieve a particular medical effect for which the therapeutic agent is intended. Examples, without limitation, of desirable medical

effects that can be attained are chemotherapy, antibiotic therapy, and regulation of metabolism. Exact dosages will vary depending upon such factors as the particular therapeutic agent and desirable medical effect, as well as patient factors such as age, sex, general condition, and the like. Those of skill in the art can readily take these factors into account and use them to establish effective therapeutic concentrations without resort to undue experimentation.

Detailed Description Text (23):
Cyclodextrin-containing liposomes are useful in extended-release drug delivery of subcutaneously administered pharmacological agents for several reasons. They are quite stable in storage. Moreover, the drug can be released over extended time periods, both in vitro and in vivo. Their sponge-like internal structure, results in efficient encapsulation into a chambers, stability in storage, and extended release in vivo. For instance, the half-life in plasma of methotrexate can be increased by 206-fold over that of free methotrexate, and with peak plasma concentration was 126-fold lower compared to unencapsulated methotrexate. As a consequence of the significant modifications of the pharmacokinetics achieved by encapsulation of a drug encapsulated in the liposome in the presence of cyclodextrin, drug potency can be increased by over 100 fold. For instance the potency of methotrexate can be increased by 130 fold through administration in accordance with the teachings of this invention, and LD.sub.50 can be decreased 110 fold. These changes in potency and LD.sub.50 indicate no significant change in therapeutic index due to introduction into the liposomes during encapsulation of the biologically active compound.

Detailed Description Text (28):
Synthesis of Multivesicular Liposome-Methotrexate-.beta.Cyclodextrin Formulation, MVL-CD-MTX

Detailed Description Text (29):
Multivesicular liposomes encapusulating methotrexate in the presence of cyclodextrin (MVL-CD-MTX) were prepared using a method described by Kim et al (Cancer Treat. Rep. 71:705, 1987) with some modifications. Briefly, for each batch of MVL-CD-MTX, the discontinuous aqueous phase consisted of 2-hydroxypropyl-.beta.-cyclodextrin solution (100 mg/ml), HCl (0.1N) and methotrexate (10 mg/ml). One ml of the discontinuous aqueous phase was added into a one dram vial containing 13.9 .mu.mol dioleoyl lecithin, 3.15 .mu.mol dipalmitoyl phosphalidy/glycerol, 22.5 .mu.mol cholesterol, 2.7 .mu.mol triolein and 1 ml chloroform. The vial was attached horizontally to the head of a vortex mixer and shaken at maximum speed for 6 minutes. One-half of the resulting "water-in-oil" emulsion was expelled rapidly through a narrow-tip Pasteur pipette into each of two 1-dram vials, each containing 2.5 ml water, glucose (32 mg/ml) and free-base lysine (40 .mu.M). Each vial was then shaken on the vortex mixer for 5 seconds at maximum speed to form chloroform spherules. The chloroform spherrule suspensions in the two vials were transferred into a 250-ml Erlenmeyer flask containing 5 ml water, glucose (32 mg/ml), and free base lysine (40 mM). A stream of nitrogen gas at 7 liter per minute was used to evaporate the chloroform over a 10-15 minute period a 37.degree. C. The MVL-CD-MTX particles were then isolated by centrifugation at 600.times.g for 5 minutes and washed three times with 0.9% NaCl solution.

Detailed Description Text (56):
With MVL-CD-MTX, neurotoxicity can be reduced by keeping most of the initial bolus of methotrexate within the multivesicular liposomes and yet tumor kill enhanced by maintaining the free methotrexate to just above the minimum cytotoxic concentration for an extended period. The present invention demonstrates the utility of cyclodextrin liposomes as a slow-releasing drug delivery system for biologically active substances, such as methotrexate. The present invention demonstrates the utility of less frequent intra-CSF administration for the prophylaxis and treatment of leptomeningeal leukemia or carcinomatosis in humans.

Detailed Description Text (81):
The in vivo studies were done on male BDF1 mice weighing 18-25 g. The group of mice was injected ip with 10 mg/kg of methotrexate in 1 ml of 0.9% NaCl as unencapsulated methotrexate control, cyclodextrin-methotrexate control (methotrexate 20 mg/ml; 2-hydroxypropyl1 -.beta.-cyclodextrin, 2 mg/ml; glucose, 6.4 mg/ml; free-base lysine, 8 mM; and HCl, 2 mM) or MVL-CD-MTX. Three mice were sacrificed and blood samples were collected from the jugular vein and placed in a heparinized tube at 0 hour (immediately after the injection), 1 hour and 4 hours after injection of the unencapsulated methotrexate or cyclodextrin-methotrexate complex; and 1, 5, 10 and 20 days after injection of MVL-CD-MTX. The plasma was separated and was kept frozen at -20.degree. C. until analyzed by the Emit.sup.R methotrexate assay on COBAS Fara Instrument. The Emit.sup.R assay is a homogeneous enzyme immunoassay technique based on the competition between drug present in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase for antibody binding sites. The limit of sensitivity was 0.02 .mu.M.

Detailed Description Paragraph Table (3):
TABLE 3 _____ Pharmacokinetic parameters of methotrexate after intraperitoneal administration Un- encapsulated MVL-CD-MTX MTX CD-MTX Free Total _____ PERITONEAL Conc. t.sub.1/2.sup.b (h) 0.54 0.46 39.6 45.6 Amount t.sub.1/2 (h) 0.45 0.41 .sup. NA.sup.d 62.4 C.sub.max.sup.c + SD 430 .+-. 13 379 .+-. 10 66.7 .+-. 18.3 1863 .+-. 168 (.mu.M) AUC (.mu.M .multidot. h) 233 316 12260 273800 PLASMA Conc. t.sub.1/2 (h) 0.9 0.6 240 NA Cmax.sup.c + SD 3.3 .+-. 0.03 3.3 .+-. 0.03 0.05 .+-. 0.05 NA (.mu.M) AUC (.mu.M .multidot. h) 11.2 12.2 18.4 NA
_____ .sup.a cyclodextrin-methotrexate .sup.b halflife .sup.c peak concentrations .sup.d not applicable

CLAIMS:

1. A liposome comprising

water,

a biologically active, eater soluble compound encapsulated within the liposome, and

a cyclodextrin in a concentration of from about 10 mg/ml to about 400 mg/ml complexed with the compound within the liposome,

wherein the biologically active compound is released from the liopsome into an aqueous solution at about 37.degree. C. at a slower rate than from a cyclodextrin-free liopsome, and without substantial compromise to the therapeutic index of the biologically active compound.

3. The liposome of claim 1, wherein the water solubility of the biologically active compound is greater that 1 .mu.g/ml in the absence of the cyclodextrin.

13. The liposome of claim 1, wherein said cyclodextrin is selected form the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers, and monosuccinyl dimethyl .beta.-cyclodextrin.

14. The liposome of claim 12, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

18. A method of increasing the half-life of a water soluble biologically active compound in an animal in need thereof comprising administering to the animal a liposome encapsulating the compound, wherein said liposome further encapsulates

water, and a cyclodextrin in a concentration from about 10 mg/ml to about 400 mg/ml complexed with said compound; whereby the half-life of the compound is substantially increased.

20. The method of claim 18, wherein water solubility of the biologically active compound is greater than 1 .mu.g/ml in the absence of the cyclodextrin, and the cyclodextrin forms an inclusion complex with the water soluble compound.

21. The method of claim 18, wherein said cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

22. The method of claim 21, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

31. The method of claim 18, wherein the cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

32. The method of claim 31, wherein the cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

33. A method of treating a pathophysiological state in an individual in need thereof comprising administering a liposome to the individual, said liposome comprising a therapeutically effective amount of a water soluble, biologically active compound complexed with a cyclodextrin, wherein the concentration of the cyclodextrin is from about 10 mg/ml to about 400 mg/ml, and the biologically active substance and the cyclodextrin are encapsulated within the liposome; whereby the half-life of the compound in the individual is substantially increased.

34. The liposome of claim 3, wherein the compound forms an inclusion complex with the cyclodextrin.

35. The method of claim 20, wherein the compound forms an inclusion complex with the cyclodextrin.

38. The method of claim 33, wherein the water solubility of the compound is greater than 1 .mu.g/ml in the absence of the cyclodextrin, and the cyclodextrin forms an inclusion complex with the water soluble compound.

47. The method of claim 33, wherein said cyclodextrin is selected from the group consisting of .alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrins, methyl cyclodextrin, ethyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin, branched cyclodextrin, cyclodextrin polymers and monosuccinyl dimethyl .beta.-cyclodextrin.

48. The method of claim 47, wherein said cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin.

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DOCUMENT-IDENTIFIER: US 5288498 A
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TITLE: Compositions of oral nondissolvable matrixes for transmucosal administration of medicaments

Detailed Description Text (88):
The present invention has applicability to a variety of drugs affecting the central nervous system. For example, the present invention may easily be utilized in the administration of opioid agonists (such as fentanyl, alfentanil, sufentanil, lofentanil, and carfentanil), opioid antagonists (such as naloxone and nalbuphene), butyrophenones (such as droperidol and haloperidol); benzodiazepines (such as valium, midazolam, triazolam, oxazolam, and lorazepam); GABA stimulators (such as etomidate); barbiturates (such as thiopental, methohexital, thiamazol, pentobarbital, and hexobarbital); di-isopropylphenols drugs (such as diprivan); and other central nervous system-acting drugs such as levodopa. It will be appreciated that other drugs may also be utilized within the scope of the present invention either singly or in combination.

Detailed Description Paragraph Table (2):
TABLE 1 GENERIC DRUG DRUG CLASS DOSE RANGE methohexital barbiturate 10-500 mg pentobarbital barbiturate 50-200 mg thiamylal barbiturate 10-500 mg thiopental barbiturate 50-500 mg fentanyl opioid agonist 0.05-5 mg alfentanil opioid agonist 0.5-50 mg sufentanil opioid agonist 5-500 .mu.g lofentanil opioid agonist 0.1-100 .mu.g carfentanil opioid agonist 0.2-100 .mu.g naloxone opioid antagonist 0.5-5 mg nalbuphene opioid antagonist 1-50 mg diazepam benzodiazepine 1-40 mg lorazepam benzodiazepine 1-4 mg midazolam benzodiazepine 0.5-25 mg oxazepam benzodiazepine 5-40 mg triazolam benzodiazepine 250-1000 mg droperidol buterophenone 1-20 mg haloperidol buterophenone 0.5-10 mg propanidid eugenol 1-10 mg etomidate GABA stimulator 5-60 mg propofol substituted phenol 3-50 mg ketamine phencyclidine 5-300 mg diprivan substituted phenol 5-20 mg

CLAIMS:

20. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the drug is fentanyl.

191. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 163, wherein the permeation enhancer is 2-hydroxypropyl-.beta.-cyclodextrin.